REMARKS

Status Summary

The request for continued examination (RCE) filed on September 26, 2003, has been entered. Claims 1, 3-5, 7, and 51-60 are pending in the application and were examined. Claims 1, 7, 51 and 55 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Maloney et al. (1997) *Blood* 90:2188-2195 (Maloney). Claims 1, 5, 7, 51, 54 and 55 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Maloney in view of U.S. Patent No. 5,626,845 to Yoneda et al. (Yoneda). Claims 1, 3-5, 7 and 51-60 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 5,776,456 to Anderson et al. (Anderson) in view of U.S. 6,042,826 to Caligiuri et al. (Caligiuri), and further in view of DeAngelis (1998) *J Neurooncology* 38:245-252 (DeAngelis). Claims 1, 3-5, 7, and 51-60 are rejected based on non-statutory obviousness-type double patenting as allegedly unpatentable over claim 1 in U.S. Patent No. 5,776,456 to Anderson et al. (Anderson).

Claims 1, 3-5, 7, and 51-55 are canceled. Claim 60 is amended to clarify claim language. New claims 61-67 are added. Reconsideration in view of the claim amendments and following remarks is respectfully requested.

Information Disclosure Statement

An Information Disclosure Statement (IDS) was filed on December 24, 2003, after issuance of the present official action. Receipt of the IDS is acknowledged in the USPTO Patent Application Information Retrieval (PAIR) database. Applicants request that the examiner acknowledge consideration of the references cited therein by marking his initials next to each document listed on the submitted PTO-1449 form and returning the same to the applicants.

Rejection of Claims Under 35 U.S.C. § 102(b)

Claims 1, 7, 51 and 55 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Maloney et al. (1997) *Blood* 90:2188-2195 (Maloney). Official action, page 2. Maloney describes anti-CD20 therapy in patients with relapsed low-grade non-Hodgkin's lymphoma, which the examiner alleges includes CNS lymphomas. The examiner has rejected applicant's arguments that CNS lymphomas are pathologically distinct from systemic lymphomas and

require distinct therapeutic approaches as unpersuasive. In the view of the examiner, the applicant has not provided evidence to conclude that the treated non-Hodgkin's lymphoma as described by Maloney is not inclusive of a CNS lymphoma. This rejection is respectfully traversed.

Claims 1, 7, 51, and 55 are canceled in favor of other pending claims, and thus the rejection of claims under § 102(b) is rendered moot. The cancellation of claims has been undertaken to expedite prosecution and does not in any way state or imply agreement with the examiner's position.

First Rejection of Claims Under 35 U.S.C. § 103(a)

Claims 1, 5, 7, 51, 54 and 55 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Maloney in view of U.S. Patent No. 5,626,845 to Yoneda et al. (Yoneda). Official action, page 3. This rejection is respectfully traversed.

Claims 1, 5, 7, 51, 54 and 55 are canceled in favor of other pending claims, and thus the rejection of claims under § 103(a) based on Maloney and Yoneda is rendered moot. The cancellation of claims is requested to facilitate prosecution and does not in any way state or imply agreement with the examiner's position.

Second Rejection of Claims Under 35 U.S.C. § 103(a)

Claims 1, 3-5, 7 and 51-60 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 5,776,456 to Anderson et al. (Anderson) in view of U.S. 6,042,826 to Caligiuri et al. (Caligiuri), and further in view of DeAngelis (1998) *J Neurooncology* 38:245-252 (DeAngelis). Official action, pages 3-5. This rejection is also respectfully traversed.

The examiner bears the burden of presenting a *prima facie* case for obviousness, which requires: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) the teaching or suggestion of all the claim limitations of the applicant's invention in the combined prior art references; and (3) a reasonable expectation of success. MPEP § 2143. Applicant responds that the examiner has failed to meet this burden given the lack of a reasonable chance of success in practicing the claimed invention.

Where the cited documents do not expressly suggest the claimed invention, the examiner is required to show how and why the applicants would have been motivated to

combine the references in the manner combined by the examiner. Although the motivation to combine prior art does not have to be expressly stated in the references themselves, "the examiner must present a convincing line of reasoning" for a proper conclusion that an invention is obvious in view of prior art. *See In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). *See also, Ex parte Clapp,* 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). Motivation relies on a reasonable expectation of success.

In contrast to the examiner's assertion, the cited documents do not describe, suggest, or motivate methods for treating a central nervous system (CNS) lymphoma by administering an anti-CD20 antibody such that levels of the anti-CD20 antibody are greater in cerebrospinal fluid (CSF) than in serum. Applicants further submit that, at the time of filing the instant application, a skilled artisan would not have had a reasonable chance of success in practicing the claimed invention.

Anderson describes methods for treatment of B cell lymphoma via administration of anti-CD20 antibodies. The examiner notes that Anderson does not teach treatment of CNS lymphomas, as now claimed. The examiner concludes that it would have been *prima facie* obvious to modify the methods of Anderson to "include B-cell lymphomas of the central nervous system because such lymphomas merely represent species of the broadly claimed genus of B-cell lymphomas." First official action (paper no. 7), pages 10-12.

The examiner relies on Caligiuri as teaching that primary CNS lymphomas involve the meninges, and on DeAngelis as teaching that lymphomas are a common cause of leptomeningeal metastasis. Based thereon, the examiner concludes that one of ordinary skill in the art would reasonably expect that a subpopulation of patients with CNS lymphoma would also exhibit leptomeningeal lymphoma. Official action, pages 3-5. The examiner also relies on Caligiuri and DeAngelis as teaching combination of immunotherapy with chemotherapy, as in claims 4, 53, and 58. Official action, pages 4-5, bridging paragraph.

In response to the rejection of claims, applicants initially request cancellation of claims 1, 3-5, 7, and 51-55 without prejudice. The rejection with respect to these claims is therefore moot.

Previously presented claims 56-60 are directed to methods for treating a central nervous system (CNS) lymphoma by administering an anti-CD20 antibody or fragment thereof, whereby levels of the anti-CD20 antibody are greater in cerebrospinal fluid (CSF) than in serum.

With respect to the pending claims, applicants submit that a *prima facie* case has not been made in that the examiner a skilled artisan would not have a reasonable chance of success in practicing the claimed invention. The examiner states that although the prior art does not specifically characterize the administered antibody is present at higher levels in CSF than in serum, this observation is obvious based on distribution of the antibodies in the CSF. Official action, page 5, lines 7-10. The examiner does not offer any facts or reference to any document to support this conclusion.

Contrary to the suggestion of the examiner, routine techniques for administration of antibodies simply do not result in levels of antibody that are higher in cerebrospinal fluid than in serum, as now claimed. In support thereof, applicants enclose a copy of Pels et al. (2003) *Onkologie* 26(4):351-354, which states that antibody concentrations in the cerebrospinal fluid are low after routine systemic administration. *See* abstract. Also enclosed is a copy of Harjunpää et al. (2001) *Leukemia and Lymphoma* 42(4):731-738, which states that an intact blood-brain barrier restricts antibody entry into the CNS. Following intravenous administration, antibody levels in the serum were over 700 times (400 μg/ml) antibody levels in the cerebrospinal fluid (0.55 μg/ml). *See* abstract. Still further, Rubenstein et al. (2003) *Blood* 101(2):466-468 describes that antibody levels in cerebrospinal fluid are approximately 0.1% of serum levels when administered intravenously. *See* abstract. It is the applicant's position that these studies clearly demonstrate that administration of anti-CD20 antibody to achieve antibody levels that are elevated in cerebrospinal fluid when compared to serum were not obvious as of the filing date.

Applicants further submit that intrathecal administration techniques do not predictably result in drug levels in cerebrospinal fluid that are higher than serum levels. For example, intralumbar administration (one type of intrathecal administration) is associated with limited drug distribution at the site of injection. Intraventricular administration is also associated with risks including infection, misplacement or occlusion of the catheter, and infectious meningitis. *See e.g.*, Cokgor et al. (2002) *J Neuro-Oncol* 60:79-88, page 81, col. 1, ¶ 4 (copy enclosed). In addition, the administered antibodies may be metabolized or eliminated from the intrathecal space. Other factors that compromise achievement of elevated levels of antibody in cerebrospinal fluid include the volume of cerebrospinal fluid and the presence of leptomeningeal disease. *See e.g.*, Blaney et al. (2000) *Med Oncol* 17:151-162, pages 156-7,

bridging paragraph (copy enclosed). Thus, prior to the disclosure of the instant application, one could not reasonably predict that elevated levels of anti-CD20 antibody in cerebrospinal fluid could be achieved. In the absence of a reasonable chance of success in practicing the invention, the claims are not *prima facie* obvious.

Based on the foregoing arguments, applicant believes that claims 56-60 fully comply with the requirements of 35 U.S.C. § 103(a) and request that the rejection of claims 56-60 based on Anderson, Caligiuri, and DeAngelis be withdrawn.

Rejection of Claims Based on Non-Statutory Obviousness-Type Double Patenting

Claims 1, 3-5, 7, and 51-60 are rejected based on non-statutory obviousness-type double patenting as allegedly unpatentable over claim 1 in U.S. Patent No. 5,776,456 to Anderson et al. (Anderson). Official action, page 5, second paragraph, through page 7. This rejection is respectfully traversed.

Based on the arguments set forth above in response to the rejection of claims under 35 U.S.C. § 103(a), which are incorporated herein, applicant believes that the methods of the present disclosure are non-obvious in view of Anderson. As such, applicant also requests that the obviousness-type double patenting rejection be withdrawn.

Discussion of New Claims

New claims 61-67 are added to more particularly claim aspects of the invention. The new claims ultimately depend from claim 56 and are believed to be patentable over Anderson, Caligiuri, and DeAngelis in view of the foregoing comments with respect to the rejection of claims 56-60 based on these documents. Support for the new claims can be found in the originally filed application, including at page 10, lines 1-4, wherein it is described that an anti-CD20 antibody can be administered intrathecally or intraventricularly; at page 65, lines 29-30, wherein it is described that therapeutic end points include morphometric and histologic correlates of anti-lymphoma activity, *e.g.*, inhibition of tumor growth; at page 19, lines 7-10, and at page 53, lines 24-30, wherein it is described that antibodies useful in the disclosed methods include chimeric antibodies, such as antibodies having non-human variable regions and human constant regions; at page 19, lines 11-29, wherein it is described that humanized antibodies comprising the antigen binding domain of a monoclonal antibody can also be used in the disclosed methods; at page 19, line 11, through page 20, line 10,

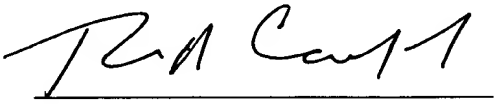
wherein the antigen binding domain of an antibody is defined by reference to complementarity determining regions and hypervariable residues of an antibody sequence; at page 20, lines 15-18, wherein it is stated that the content of U.S. Patent No. 5,736,137, which discloses the sequence of the rituximab heavy chain and light chain variable regions and which identifies the complementarity determining regions of the rituximab antibody, is incorporated into the instant application; and in the examples, beginning at page 64, line 16, which describes use of the rituximab antibody.

Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

PILLSBURY WINTHROP LLP



Thomas A. Cawley, Jr., Ph.D.
Registration No. 40,944

P.O. Box 10500
McLean, VA 22102
(703) 905-2144 Direct Dial
(703) 905-2500 Facsimile

Date: May 12, 2004

TAC/JBM